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**Datasheet for the decision
of 11 March 2016**

Case Number: T 0371/12 - 3.3.07

Application Number: 05758582.0

Publication Number: 1768649

IPC: A61K9/08, A61K31/495

Language of the proceedings: EN

Title of invention:

PHARMACEUTICAL COMPOSITION OF PIPERAZINE DERIVATIVES

Patent Proprietor:

UCB FARCHIM S.A.

Opponent:

Zentiva k.s.

Relevant legal provisions:

EPC Art. 56

RPBA Art. 13(1), 13(3)

Keyword:

Inventive step - main request, auxiliary request 1 and
auxiliary request 2 (no)
Late-filed auxiliary requests 3 and 4 - admitted (no)



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Case Number: T 0371/12 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 11 March 2016

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Decision under appeal: **Decision of the Opposition Division of the
European Patent Office posted on 22 December
2011 revoking European patent No. 1768649
pursuant to Article 101(3) (b) EPC.**

Composition of the Board:

Chairman J. Riolo
Members: A. Usuelli
D. T. Keeling

Summary of Facts and Submissions

- I. European patent No. 1 768 649, based on European application 05758582.0, was granted on the basis of seven claims.

Claim 1 as granted read as follows:

"1. A liquid pharmaceutical composition comprising an active substance chosen among cetirizine, levocetirizine and efletirizine, and at least one preservative, wherein the amount of preservative is in the case of parahydroxybenzoate esters more than 0 and less than 1.5 mg/ml of the composition, the preservative being selected from the group of methyl parahydroxybenzoate, ethyl parahydroxybenzoate, propyl parahydroxybenzoate, a mixture of methyl parahydroxybenzoate and ethyl parahydroxybenzoate or propyl parahydroxybenzoate, and a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate".

- II. An opposition was filed against the patent on the grounds that its subject-matter lacked novelty and inventive step (Article 100(a) EPC). The following documents were among those cited during the first-instance proceedings:

D1: EP 605203 A2

D3: Handbook of Pharmaceutical Excipients, 3rd Ed. 2000, pages 340-342 and 450-453

D4: Allergy 2001, 56:339-343

- III. By decision posted on 22 December 2011, the opposition division revoked the patent. The decision was based on the patent as granted as main request and on two

auxiliary requests filed on 19 October 2010 (auxiliary request 1) and 29 September 2011 (auxiliary request 2).

IV. With regard to the requirement of inventive step, the opposition division came to the following conclusions:

- a) Document D1, representing the closest prior art, disclosed in example 5 a composition comprising *inter alia* cetirizine hydrochloride and 3 mg/ml of a mixture of parahydroxybenzoates (parabens). The composition defined in claim 1 of the patent in suit differed from this composition in that it contained a lower concentration of parabens, i.e. more than 0 and less than 1.5 mg/ml.

The patent did not contain any data supporting the alleged effect of reducing the risk of allergic reactions. Furthermore, it was not convincingly shown that the problem of providing compositions having the recommended efficacy of antimicrobial preservation, was actually solved over the whole scope of the claim. Hence, the technical problem was to be defined as the provision of further liquid "compositions of cetirizine, levocetirizin or efletirizine comprising parabens showing (some degree of) antimicrobial effectiveness".

Document D3 disclosed the standard concentrations of methylparaben and propylparaben when used in the antimicrobial preservation of ophthalmic, nasal and oral solutions. The ranges of concentrations disclosed in this document overlapped with the range recited in claim 1 of the patent in suit. The skilled person faced with the technical problem would have modified the amount of parabens of the composition of D1 in the

light of the teaching of D3 thereby obtaining compositions falling in claim 1 of the patent in suit. Hence, the main request did not comply with the requirements of Article 56 EPC.

- b) The limitations introduced in the auxiliary requests did not change the assessment of inventive step. In particular, the use of levocetirizine instead of racemic cetirizine was obvious in view D4, which indicated that the pure enantiomer had more therapeutic activity than the racemic mixture and hence it could be used in lower amount. Thus, auxiliary requests 1 and 2 were not inventive either.

- V. The patent proprietor (appellant) lodged an appeal against that decision. With the statement setting out the grounds of appeal filed on 23 April 2012 the appellant maintained the main request (i.e. maintenance of the patent as granted) and submitted two auxiliary requests. Additionally, with the same letter it submitted the following document:

D17: Supplementary examples

- VI. The Board issued a communication pursuant to Article 15(1) RPBA on 4 November 2015. In relation to inventive step, the Board agreed with the appealed decision that document D1 represented the closest prior art and that the pharmaceutical composition claimed in the patent differed from the composition of example 5 of D1 in the lower concentration of parabens. Furthermore, the Board observed that according to document D3, the parabens could be used in concentrations which were below the concentration in which these substances were present in

the composition of D1 and within the range of claim 1 of the patent.

As to the auxiliary requests the Board indicated that these appeared to extend the protection conferred by the patent.

VII. By letter dated 11 February 2016, the appellant withdrew the auxiliary requests submitted on 23 April 2012 and filed four new auxiliary requests.

Claim 1 of auxiliary request 1 read as follows:

"1. A liquid pharmaceutical composition comprising the active substance levocetirizine, wherein the pharmaceutical composition contains an amount of p-hydroxy-benzoate esters selected in the range of 0.01 and 1.125 mg/ml of the composition, where the p-hydroxy benzoate esters are methyl p-hydroxybenzoate/ propyl p-hydroxybenzoate in a ratio of 9/1 expressed in weight".

Claim 1 of auxiliary request 2 differed from claim 1 of auxiliary request 1 in that the lowest concentration of parabens was set at 0.1 mg/ml instead of 0.01 mg/ml.

Claim 1 of auxiliary requests 3 and 4 were based on the corresponding claims of respectively auxiliary request 1 and auxiliary request 2 but differed therefrom in the indication that the composition was in the form of an oral solution.

VIII. Oral proceedings were held on 11 March 2016.

IX. As far as relevant for the present decision, the arguments of the appellant can be summarized as follows:

- a) Inventive activity - Main request and auxiliary requests 1 and 2

Document D1 was the closest prior art. This document disclosed in example 5 an ophthalmic composition comprising cetirizine and a mixture of methyl- and propylparaben. The composition claimed in the patent in suit differed from this composition of D1 in that it contained a lower amount of parabens. Starting from the closest prior art the technical problem was to be seen in the provision of a composition comprising cetirizine, levocetirizine or efletirizine as active ingredient, presenting a reduced risk of allergic reactions and at the same time maintaining a sufficient capacity to resist antimicrobial contamination. Examples 1 and 2 of the patent demonstrated the antimicrobial effect of cetirizine and levocetirizine compositions which did not contain parabens. It was clear from comparative examples 1 and 2 of D17 that this effect was not due to the presence of sodium acetate, which was not active against some microorganisms. Hence, the antimicrobial properties of the compositions of examples 1 and 2 of the patent in suit were due to the active ingredients. Thanks to these antimicrobial properties it was possible to reduce the amount of parabens in the composition. None of the prior art documents suggested that cetirizine and the other active ingredients had antimicrobial properties.

Document D1 did not address problems concerning the preservation of the compositions. Moreover, in the most part of the examples of this document the preservative agent used was not a paraben and some examples did not contain any preservative agent at all. Thus, the skilled person had no reason to consider in particular the composition of example 5. As to document D3, the lower

amounts of parabens suggested in the table of section 7 were purely theoretical. It was clear from Table 1 that these amounts were not sufficient to provide an adequate protection against microbial contamination. Document D3 appeared therefore to provide inconsistent information. Furthermore, this document suggested to use a combination of different parabens. Hence, the amounts reported in section 7 for methylparaben were to be considered in combination with additional amounts of other parabens. Therefore, the compositions of the patent in suit were not suggested by the combined teaching of D1 and D3.

The compositions of the auxiliary requests were more restricted in terms of active ingredient and amounts of parabens used. The arguments submitted in respect to the main request applied also to the auxiliary requests.

b) Admittance of auxiliary requests 3 and 4

The subject-matter of these requests was restricted to compositions in the form of oral solution. This limitation was included also in granted claim 7. These requests were therefore to be admitted into the appeal proceedings.

X. As far as relevant for the present decision, the arguments of the respondent can be summarized as follows:

a) Inventive activity - Main request and auxiliary requests 1 and 2

The compositions of the patent in suit differed from the composition disclosed in example 5 of D1 on account of the lower concentration of parabens. There was no

evidence supporting the claim that the compositions of the patent in suit caused less adverse reactions. There were also no tests showing the antimicrobial activity of the active ingredients because the compositions tested in the patent and in D17 contained not only cetirizine or levocetirizine but also some preservative agents. The technical problem formulated by the opposition division was therefore correct. The skilled person studying the ophthalmic composition of example 5 of D1 would have considered the information disclosed in section 7 of D3 as to the suitable amounts of parabens in compositions for ophthalmic use. These amounts overlapped with the concentration range defined in claim 1 of the patent in suit. Accordingly, the composition of the patent in suit was obvious in view of the teaching of D1 in combination with D3. Concerning the data disclosed in Table 1 of D3, these referred to the activity of solutions containing only methyl (or propyl) paraben. However, the antimicrobial properties of a pharmaceutical composition were influenced by all the components present in the compositions. Hence, the skilled person would have attributed more weight to the data in section 7 of D3 rather than the data in Table I.

The same arguments applied to the subject-matter of auxiliary requests 1 and 2.

b) Admittance of auxiliary requests 3 and 4

The restriction to compositions in the form of oral solution represented an inadmissible shift of the invention. The appellant had never submitted arguments on inventive step based on the relevance of this specific pharmaceutical form. Accordingly, auxiliary requests 3 and 4 were not to be admitted into the appeal proceedings.

XI. The appellant requested that the decision under appeal be set aside and that the patent be maintained according to the main request submitted on 23 April 2012, corresponding to the patent as granted, or that the patent be maintained according to one of the four auxiliary requests submitted on 11 February 2016.

XII. The respondent requested that the appeal be dismissed.

Reasons for the Decision

Main request (granted patent)

1. Inventive step

The patent in suit relates to pharmaceutical compositions capable of resisting microbial contamination, which contain as active ingredient a substance selected from cetirizine, levocetirizine and efletirizine ([0006] to [0009]).

1.1 Closest prior art

1.1.1 In agreement with the appealed decision, the Board considers that document D1 represents the closest prior art.

This document relates to antiallergic compositions for ophthalmic and nasal use containing citirizine as active ingredient. Although the main problem addressed in D1 concerns the stability of the composition, this document discusses on page 3 (lines 51 to 57) also the need of adding preservative agents, such as parabens, to the citirizine compositions.

1.1.2 Among the compositions disclosed in the eight examples of D1, the composition of example 5 is the one with the most features in common with the subject-matter of claim 1 in that it is the only one containing parabens. Thus, within the disclosure of the closest prior art, example 5 is the most promising starting point to be considered for assessing whether the subject-matter of claim 1 involves an inventive step.

1.1.3 The composition of the patent in suit differs from the composition of example 5 of D1 in the amount of parabens, which is "more than 0 and less than 1.5 mg/ml", whereas in the composition of D1 the parabens concentration is 3 mg/ml.

1.2 Technical problem

1.2.1 In paragraph [0007] of the description it is explained that the invention underlying the patent in suit is based on the recognition that the antihistaminic agents belonging to the family of substituted benzhydryl piperazines, such as cetirizine, levocetirzine and efletirizine, possess antimicrobial properties in aqueous solutions. This makes it possible to reduce the amount of preservative agents in the liquid formulations of these active ingredients. When the preservative agents are parabens, the reduction of concentration leads to a decrease of the risk of allergic reactions in sensitive patients.

Hence, the pharmaceutical compositions claimed in the patent in suit should be safer than the composition of D1 on account of a reduced amount of parabens but at the same time they should maintain an adequate capacity to resist microbial contamination.

- 1.2.2 The patent does not contain any experimental data supporting the effect of a reduction of the risk of allergic reactions in sensitive patients.

It is however noted that D3 reports that methylparaben and propylparaben may be irritant to the skin, eye and mucous membranes. It is furthermore stated that hypersensitivity reactions to parabens, appearing as contact dermatitis, have been reported (sections "Safety" and "Handling precautions" on pages 342 and 452).

In the light of this general knowledge as to the potential side-effects associated with the use of parabens, the Board considers credible, even in the absence of any experimental evidence, that the composition of the patent in suit causes fewer allergic reactions than the composition of example 5 of D1 because it contains a reduced amount of parabens.

- 1.2.3 As to the antimicrobial properties of the compositions, the following is observed.

Examples 1 and 2 of the patent show the antimicrobial properties of cetirizine and levocetirizine compositions which do not contain any paraben. The objective of the experiments described in these examples is to demonstrate that the active ingredients have themselves a preservative effect.

The efficacy of antimicrobial preservation of compositions according to claim 1 of the patent in suit comprising variable amounts of parabens is illustrated in examples 3 to 9 of the patent and in example 3 of D17.

Based on this evidence the Board accepts that the composition of the patent in suit maintains an adequate capacity of resisting microbial contamination.

1.2.4 The technical problem is therefore formulated as the provision of a liquid pharmaceutical composition comprising cetirizine, levocetirizine or efletirizine as active ingredient and parabens as preservative agents, which composition presents a reduced risk of allergic reactions and is capable of resisting microbial contamination.

1.3 Obviousness

1.3.1 Document D3 is an extract of an handbook relating to pharmaceutical excipients. It is divided in two parts which concern the products methylparaben and propylparaben.

In section 7 of the part concerning methylparaben it is reported that this substance is widely used as an antimicrobial preservative. In the same section it is indicated that in ophthalmic preparations and in oral solutions methylparaben is used in a concentration of 0.015 to 0.2 %, which corresponds to 0.15 to 2 mg/ml.

Similar information is disclosed in section 7 of the second part of D3, in relation to propylparaben. It is indicated that as an antimicrobial preservative, propylparaben is used in ophthalmic preparations in a concentration of 0.005 to 0.01 % (corresponding to 0.05 to 0.1 mg/ml) and in oral solutions in concentrations of 0.01 to 0.02 % (corresponding to 0.1 to 0.2 mg/ml).

1.3.2 The concentrations reported above for ophthalmic and oral solutions, i.e. liquid compositions, overlap with

the range of more than 0 and less than 1.5 mg/ml recited in claim 1 of the patent in suit. Furthermore, it is also possible to combine methyl and propylparaben in amounts within the ranges disclosed for each of these substances in D3 whilst still respecting the maximum amount allowed by claim 1 (i.e. 1.5 mg/ml).

1.3.3 Document D3 also includes in each of its two parts a table, named in both parts "Table 1", disclosing the minimum inhibitory concentrations (MIC) of methylparaben and propylparaben in aqueous solutions. The tables provide the antimicrobial activity of the two preservative agents against various microorganisms, including bacteria and fungi. As remarked by the appellant, the MICs in respect of some specific microorganisms are sometimes higher than 2 mg/ml. In the appellant's opinion, the skilled person considering these data would conclude that the ranges of concentrations reported for ophthalmic and oral solution in sections 7 of D3 (see point 1.3.1 above) may not be sufficient for an effective protection against microbial contamination.

1.3.4 The Board does not share the appellant's view for the following reasons.

Document D3 indicates that the antimicrobial activity of parabens can be improved by using them in combination since synergistic effects occur (see pages 341 and 450). The activity can be enhanced also by the addition of propylene glycol, a substance which is present also in most of the compositions exemplified in the patent in suit. Other excipients reported to enhance the antimicrobial activity of parabens are phenylethyl alcohol and edetic acid. Finally, D3 indicates that the

preservative effect of the parabens is also affected by the pH.

Thus, D3 does not indicate that the parabens need necessarily to be used in concentrations equal to, or above, the MICs values reported in Table 1. As pointed out by the opposition division in its decision (point 4.2), the MICs are a measure of the antimicrobial properties of a substance which are determined under specific conditions. As such, they can be regarded as parameters that make possible an objective comparison of the antimicrobial activities of different preservative agents. No other meaning can be attributed to the MICs values.

The MICs values of parabens cannot be easily correlated to the overall antimicrobial properties of a composition comprising various substances in addition to parabens, because, as explained above, the antimicrobial properties of parabens can be enhanced in various ways, for instance by combining them and thereby obtaining a synergistic effect or by adding propylene glycol. Thus, whether a composition is sufficiently protected against microbial contamination depends on various factors such as the type of preservative agents used, their amounts and the presence of excipients such as propylene glycol. An adequate protection of a composition can therefore be obtained also using a paraben in a concentration below the MICs values reported in D3.

For these reasons, the Board considers that the skilled person reading document D3, would not see any inconsistency between the ranges of concentrations disclosed in sections 7 and the MICs data. Hence, he would have no reason for disregarding the information disclosed in sections 7 as to the usual concentration of

methylparaben and propylparaben in ophthalmic preparations and oral solutions.

- 1.3.5 As already discussed in point 1.2.2 above, document D3 also provides information concerning the safety of parabens. On pages 342 and 452 it is reported that parabens may cause hypersensitivity reactions and that they may be irritant to the skin, eyes and mucous membranes.

Hence, the skilled person concerned with the problem of improving the safety profile of the ophthalmic composition of example 5 of D1, would learn from D3 that the parabens may cause various adverse reactions. At the same time however, he would observe that the amount of parabens in the composition of D1 is much higher than the amount suggested in D3 for ophthalmic compositions. In the Board's opinion, this would prompt the skilled person to modify the composition of D1 by reducing the concentration of parabens according to the indications disclosed in sections 7 of D3, and verify whether the new composition has an improved safety profile but is still capable of resisting microbial contamination.

He would therefore arrive at the subject-matter of claim 1 without applying any inventive activity.

- 1.3.6 The appellant underlined in its submissions that the experimental data of the patent in suit and of D17 demonstrated the antimicrobial properties of the active ingredients of the composition of claim 1. These properties were neither disclosed nor suggested in the prior art.

The interpretation of these data was contested by the respondent with the argument that the compositions

tested contained additional antimicrobial agents, such as sodium acetate. It was therefore not possible to establish whether the antimicrobial activity of the composition was due to the active ingredients or to the additional antimicrobial agents.

In the Board's opinion, establishing whether, and possibly to what extent, cetirizine and the other active ingredients possess an antimicrobial effect, is not a decisive issue in the circumstances of the present case because this effect does not in any case translate into any inventive feature of claim 1.

Indeed, regardless of whether the active ingredients contribute or not to the overall antimicrobial effect of the compositions, the reduction of the amount of parabens, which represents the distinguishing feature over the closest prior art, is suggested by D3 for the reasons discussed above. Furthermore, D3 also suggests the possible advantages that can derive from a reduction of the concentration of parabens, namely an improvement of the safety profile of the composition.

Thus, the conclusion that the subject-matter of claim 1 is obvious in view of the combined teachings of D1 and D3 holds good even if it is acknowledged that the active ingredients possess antimicrobial properties and even if it is acknowledged that these properties were hitherto unobserved.

- 1.4 It follows from the above that the main request does not fulfil the requirements of Article 56 EPC.

Auxiliary request 1

2. Inventive Step

2.1 Claim 1 of this request differs from claim 1 of the granted patent in that the active ingredient is limited to levocetirizine and the parabens are present as a mixture of methyl- and propylparaben in a ratio of 9:1 and in an amount comprised between 0.1 and 1.125 mg/ml (see point VII above).

2.2 As explained in paragraph [0015] of the patent, levocetirizine is the levorotatory enantiomer of cetirizine. Document D4 reports that both compounds possess antihistaminic activity (see abstract).

The opposition division considered in its decision that the use of levocetirizine instead of racemic cetirizine was obvious in view of D4 which indicates that the levorotatory enantiomer has more therapeutic activity than the racemic form.

This conclusion was not disputed by the appellant during the appeal proceedings. Nor did it submit any argument on inventive step based on the use of levocetirizine as active ingredient.

The Board sees no reason therefore to deviate from the conclusions of the opposition division. Hence, the limitation introduced in claim 1 with regard to the active ingredient does not provide any inventive contribution to the subject-matter of the claim.

2.3 As to the limitation concerning the composition of the parabens mixture and its total amount, the Board observes that also document D3 suggests using

methylparaben together with propylparaben in a ratio of 9:1 (page 340, first paragraph of right column). Furthermore, as already observed in respect of the main request, the ranges of concentration disclosed in sections 7 of D3 for ophthalmic and oral solutions allow combining methyl- and propylparaben in a ratio 9:1 and in a total amount which is comprised in the range of concentration recited in claim 1 in suit.

It follows from the above that also the features introduced in claim 1 concerning the parabens mixture do not provide any inventive contribution to the subject-matter of the claim.

Accordingly, the subject-matter of auxiliary request 1 does not meet the requirements of inventive step.

Auxiliary request 2

3. Inventive step

3.1 Claim 1 of this request is based on claim 1 of auxiliary request 1 and it differs therefrom in that the lowest concentration of parabens is set at 0.1 mg/ml instead of 0.01 mg/ml.

This modification has no effect on the validity of the considerations set out in point 2 above, in respect of auxiliary request 1.

Thus, auxiliary request 2 fails to comply with Article 56 EPC.

Auxiliary requests 3 and 4

4. Admittance into the appeal proceedings

4.1 Auxiliary requests 3 and 4 were submitted on 11 February 2016, i.e. one month before the oral proceedings.

According to Article 13(1) RPBA, the discretion of the Board to admit amendments to a party's case is to be exercised in view of *inter alia* the complexity of the new subject-matter, the current state of the proceedings and the need for procedural economy. Furthermore, Article 13(3) RPBA provides that amendments made after oral proceedings have been arranged, as in the present case, shall not be admitted if they raise issues which the Board or the other parties cannot be expected to deal with without adjournment of oral proceedings.

4.2 The subject-matter of claim 1 of auxiliary requests 3 and 4 has been limited to compositions in the form of an oral solution.

The appellant observed that compositions in the form of oral solutions were explicitly foreseen in claim 7 of the patent.

The Board notes in this respect that in the claim referred to by the appellant, also other pharmaceutical forms, such as eye drops, were explicitly mentioned. Auxiliary requests 3 and 4 are therefore the first requests which are limited to oral solutions.

4.3 Before the filing of these requests, the appellant never submitted arguments on inventive step based on the relevance of providing compositions in the form of oral

solutions. Indeed, as is evident from the considerations set out in points 1 to 3 above, the pharmaceutical form of the composition did not play any particular role in the assessment of inventive step.

In the Board's view, the filing of new requests which are focused on a technical feature which was never regarded as a critical aspect of the claimed subject-matter, amounts to a substantial shift of the focus of the invention. Admitting these requests would require a different approach to inventive step, possibly starting from a different prior art in view of the fact that D1 relates only to ophthalmic and nasal compositions. That goes against the requirement of procedural economy and could potentially open new issues which the Board and the respondent cannot reasonably be expected to deal with without adjournment of the oral proceedings.

Thus, the Board, in the exercise of its discretion under Article 13(1) and (3) RPBA, decides not to admit auxiliary Requests 3 and 4 into the appeal proceedings.

Order

For these reasons it is decided that:

The appeal is dismissed

The Registrar:

The Chairman:



S. Fabiani

J. Riolo

Decision electronically authenticated